

BARTONELLA INFECTIONS IN HUMANS AND ANIMALS: AN UPDATE.



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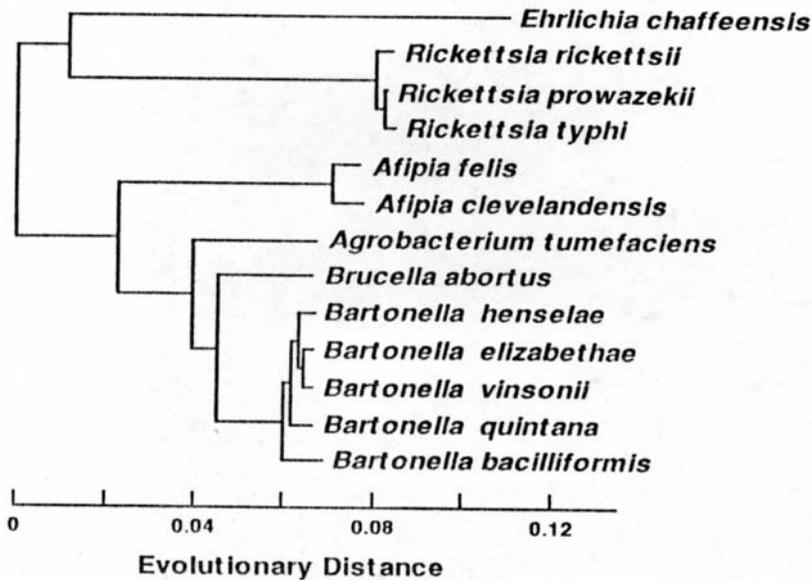
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C.D.C.: R. Regnery

and many other agencies

Alpha-Proteobacteria



Conditions Caused by *Bartonella* Species in Humans.

Bartonella sp.

Condition

<i>B. bacilliformis</i>	Carrion's disease (Oroya fever or verruga peruana)
<i>B. quintana</i>	Trench fever, endocarditis, chronic bacteremia, bacillary angiomatosis
<i>B. henselae</i>	Cat scratch disease, endocarditis, myocarditis, chronic bacteremia, neuroretinitis, arthritis, status epilepticus, bacillary angiomatosis, peliosis hepatis, prolonged fever, weight loss, glomerulonephritis, osteomyelitis...
<i>B. clarridgeiae</i>	CSD? (serological evidence only)
<i>B. elizabethae</i>	Endocarditis
<i>B. vinsonii berkhoffii</i>	Endocarditis
<i>B. grahamii</i>	Uveitis
<i>B. vinsonii arupensis</i>	Fever, confusion, underlying valvulopathy
<i>B. washoensis</i>	Cardiopathy (myocarditis?)

INSECTS ASSOCIATED or POSSIBLY ASSOCIATED WITH THE TRANSMISSION OF *BARTONELLA* spp.

SPECIES	INSECT VECTOR
<i>B. bacilliformis</i>	Sand flies (<i>Lutzomyias</i> sp.)
<i>B. quintana</i>	Human body louse (<i>Pediculus humanus corporis</i>)
<i>B. henselae</i>	Cat flea (<i>Ctenocephalides felis</i>); Ticks?
<i>B. clarridgeiae</i>	Cat flea (<i>Ctenocephalides felis</i>)??
<i>B. koehlerae</i>	Cat flea (<i>Ctenocephalides felis</i>)??
<i>B. vinsonii vinsonii</i>	Vole ear mite (<i>Trombicula microti</i>)
<i>B. vinsonii arupensis</i>	Deer tick? (<i>Ixodes scapularis</i>)??
<i>B. vinsonii berkhoffii</i>	Ticks ?? (<i>Rhipicephalus sanguineus</i> , <i>Dermacentor variabilis</i> , <i>Amblyoma americanum</i> , <i>Ixodes scapularis</i> , <i>Ixodes pacificus</i>)???
<i>B. bovis</i>	Biting flies??, ticks??

Bartonella bacilliformis infections:

Carrion Disease (Oroya fever and Verruga peruana).

- Endemic in South America, mainly Andean river valleys of Peru, (especially Rimac and Santa Eulalia river valleys), Ecuador and Colombia. Recent outbreaks discovered near Cuzco, Peru. Foci lie at right angles to the prevailing winds and at altitudes of 700 to 2500 meters where the sandfly *Lutzomyia verrucarum* lives.
- No animal reservoir known. Humans can be bacteremic for months (up to 10% of the population in endemic areas).
- Oroya fever: acute, progressive and severe anemia. 40% lethality.
- Verruga peruana: 1-2 months after acute illness or commonly without previous acute form. Miliary or nodular or deep-seated lesions.

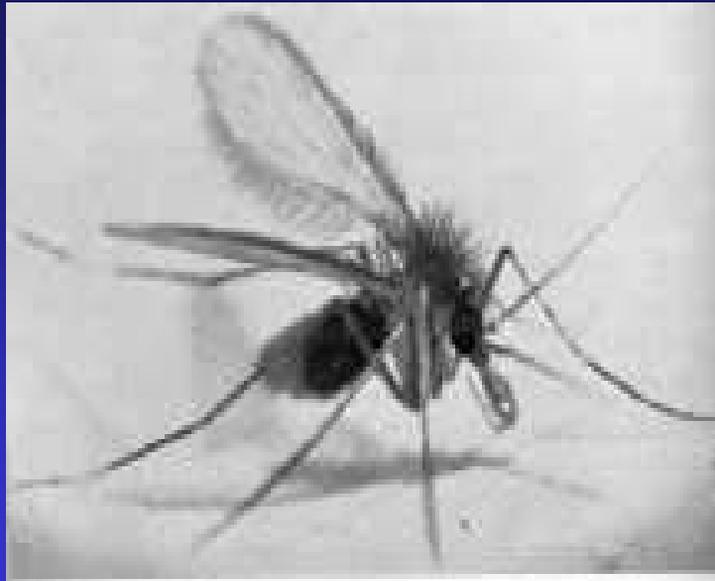
**Verruga
Peruana**



Verruga Peruana

Lutzomyia
Verrucarum
female

Bartonella
Bacilliformis
vector



Trench Fever

caused by:

Bartonella quintana

transmitted by the
human body louse
Pediculus humanus
corporis



Trench Fever, caused by *Bartonella quintana*

- **Worldwide distribution. More than 1 million soldiers during WWI infected with *B. quintana* developed trench fever.**
- **Symptoms: incubation: 15-25 days. Fever with recurrence (= 5-day or quintan fever), headache and pain in the legs.**
- **Humans only known reservoir. Asymptomatic carriers reported in homeless people in Europe and USA.**
- **Vector: Human body louse (*Pediculus humanus* var. *corporis*). Can transmit disease 5-10 after feeding on infected persons. Infective for life, *B. quintana* replicates actively in louse intestines. Transmission likely through lice feces, infectious for up to 1 year.**

*Pediculus
humanus*



**Bacillary
Angiomatosis**



**Bacillary
Angiomatosis**

**Cutaneous
Lesion**



Source: Dr. Jane Koehler, UCSF

Bacillary

Angiomatosis

Source: Dr. F. A. Murphy



Bartonella
Henselae



Source: Dr. Jane Koehler, UCSF

High rate of *Bartonella henselae* infection in HIV-positive outpatients in Johannesburg, South Africa.

Frean et al., *Trans. Royal Soc. Trop Med. Hyg.*, 2002;96:549-550.

- Non-random survey of outpatients attending HIV clinics in Johannesburg, South Africa.
- 188 patients sampled, of whom 19 (10.1%) were PCR positive for *B. henselae*.
- Only 1 patient had a suspected diagnosis of bacillary angiomatosis. 13 of the 19 were tested serologically and 8/13 (62%) were seropositive (1:64 or higher).
- By comparison, 2 (1%) of 204 blood cultures from HIV positive patients were positive for *B. henselae* (Clarridge et al., *J. Clin. Microbiol.* 1995;33:2107-2113).

Cat Scratch Disease (*Bartonella henselae*)

Epidemiology: Cats are the main reservoir (28% of US pet cats sero +).

Cats can be bacteremic for months. Stray cats, young cats more likely to be bacteremic. No vertical/horizontal transmission.

Fleas are main vector from cat to cat. Cat to humans: mainly scratch, likely inoculation of infective flea feces at time of scratch. Flea transmission to humans possible, not clearly demonstrated. Recent suggestion of possible tick transmission.

Symptoms: 1 week after scratch: papule/vesicle at inoculation site,
2-3 weeks: lymphadenopathy, fever,

Complications: Parinaud's syndrome, granulomatous lesions, retinitis, endocarditis, encephalitis (1 lethal case).

Diagnosis: in humans, mainly serology; in cats: blood culture/PCR

Treatment: No benefit in classical forms. In severe cases, Doxycycline, Erythromycin, Rifampin, Azithromycin: 15- 21 days.

CAT-SCRATCH DISEASE



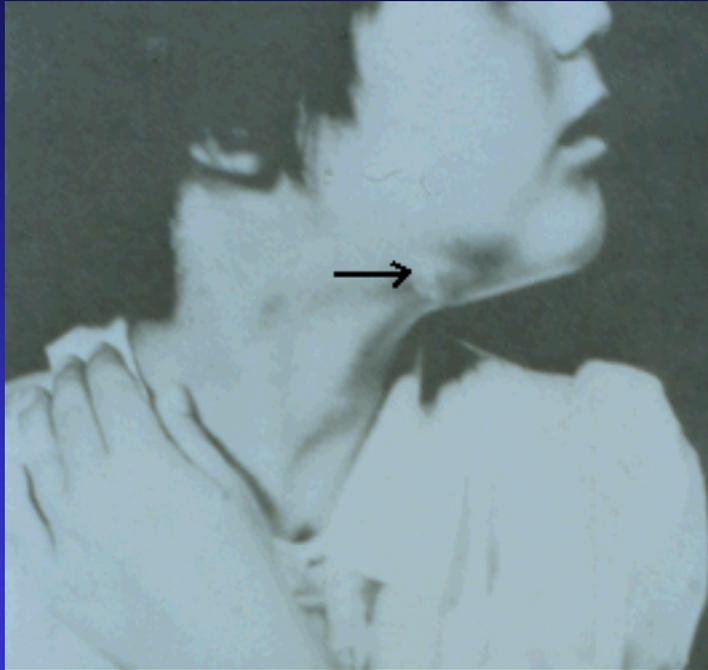
Figure 2. The primary inoculation papule of cat-scratch disease occurs three to 10 days after injury. The lesion has usually disappeared by the time symptoms develop. (Photograph courtesy of Churchill Livingstone, Inc.)

Cat Scratch Disease

Vesicle at inoculation site



**Cat Scratch
Disease**



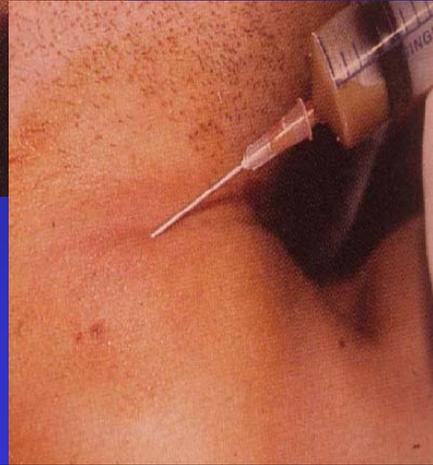
**Cat Scratch
Disease**



Cat

Scratch

Disease



Cat Scratch Disease: Analysis of 130 seropositive cases

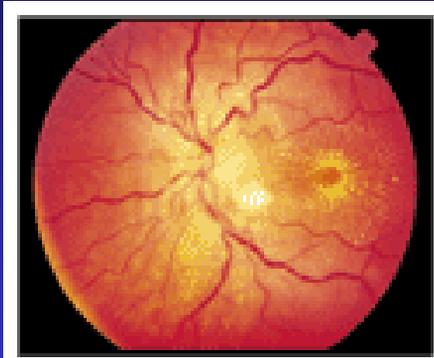
(Murakami et al., J. Infect. Chemother. 2002;8:349-352)

- **In Japan, cases occurred mainly in Fall and Winter.**
- **80% were < 18 years old.**
- **Regional lymphadenopathy in 85% (110/130) of the patients neck (33%), axillary (27%), inguinal (18%)**
- **Main symptoms were: fever, headache and malaise (77%)**
Typical syndrome: **80% (103/130);**
Atypical: **20% (27)**
fever of unknown origin (37%);
neuroretinitis (22%), encephalopathy (15%),
hepatosplenic granuloma (11%) and Parinaud's
oculoglandular syndrome (7.5%).
- **Fever of unknown origin or lasting > 14 days in 27 cases (21%), of which 11 (41%) lacked lymphadenopathy.**

Cat Scratch Disease

Optic Neuritis Due to *Bartonella henselae* Infection

A 14-year-old girl presented with worsening headaches, unilateral decreased visual acuity (20/20 [right eye] and 5/200 [left eye]), and ocular pain in the left eye. A retinal examination showed bilateral optic-disk elevation with edema, lipid exudates that formed a macular star, and an area of choroiditis surrounded by serous fluid. IFA titers of antibodies against *Bartonella henselae* were 1:160 or more for IgM and 1:512 or more for IgG. The patient owned a cat but did not recall a specific scratch. Source: Herz & Lahay. N.Engl. J. Med. 2004; 350:e1.



***Bartonella henselae* infection associated with neuroretinitis, central retinal artery and vein occlusion, neovascular glaucoma, and severe vision loss.**

A 21-year-old man had no light perception in the left eye secondary to concurrent central retinal artery and vein occlusion believed to have resulted from infection with *Bartonella henselae*. Forty days later, he developed neovascular glaucoma in the left eye.



One month after presentation, color fundus photograph of the left eye reveals optic disk edema, dilated and tortuous retinal veins, intraretinal hemorrhages in all four quadrants, and retinal pallor.

Source: Gray et al. Am J Ophthalmol. 2004; 137: 187-189.

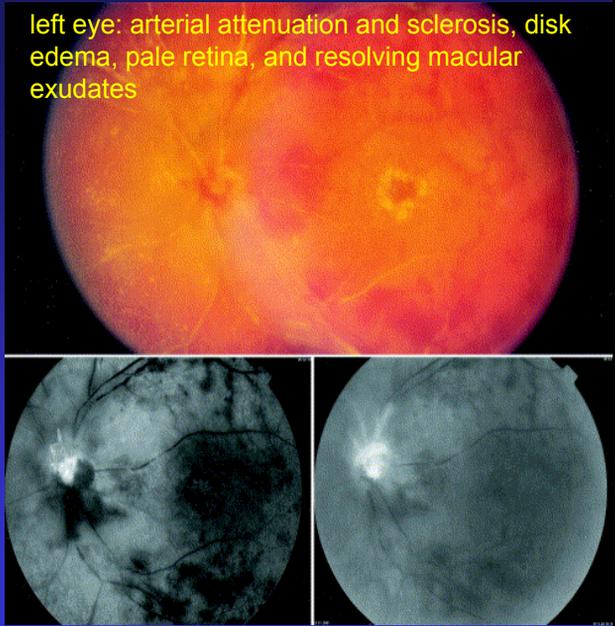
Bartonella henselae infection associated with neuroretinitis, central retinal artery and vein occlusion, neovascular glaucoma, and severe vision loss.

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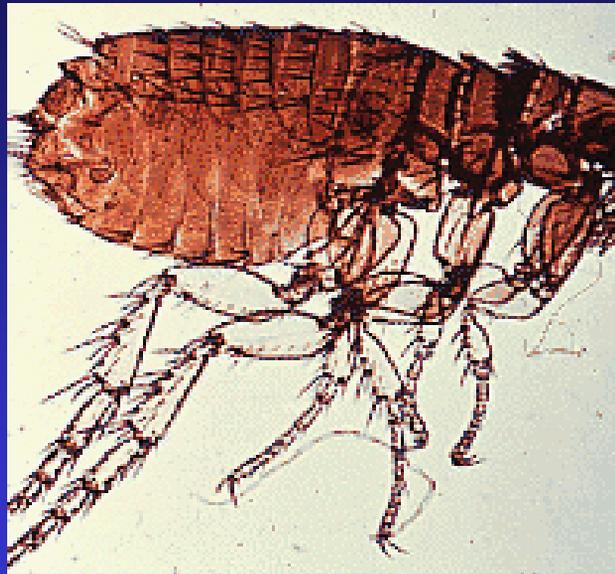
Left: Fluorescein angiogram reveals absent retinal arterial fluorescence with background choroidal fluorescence.

Right: minimal filling of the superior juxtapapillary vasculature

left eye: arterial attenuation and sclerosis, disk edema, pale retina, and resolving macular exudates



Ctenocephalides felis



Persistent *Bartonella* bacteremia in humans.

B. bacilliformis

5 to 10 % of people in an endemic area of Peru were found to be bacteremic without evidence of clinical signs ([Weiman and Pinkerton, 1937, Proc. Soc. Exp. Biol. Med. 37:596-598](#)).

B. quintana

Experimentally infected volunteers bacteremic for as many as 300 to 443 days after onset of Trench fever ([Swift, 1920, Arch Inter. Med. 26:76-98](#)). Asymptomatic carriers described in the 1940s.

In a recent urban outbreak in Marseilles, France, 14% of 71 homeless persons were bacteremic for *B. quintana*, and of those bacteremic patients 80% were afebrile ([Brouqui et al., N. Engl. J. Med. 1999;340:184-189](#)).

B. henselae

A few human cases of persistent bacteremia in immunocompetent persons have been reported ([reviewed by Koehler, 2000](#)).

Rheumatic manifestations related to *Bartonella* infection in humans

Symptoms/ syndromes	Agent	PCR/Serol	Source
Erythema nodosum	?	clinical	Carithers. Am. J. Dis. Child, 1985;139: 1124-1133.
Leukoclastic vasculitis	<i>B. henselae</i>	Serol.	Hashkes et al., 1996, Pediatr. Infect. Dis J. 15;93-95.
Myositis	<i>B. henselae</i>	Serol.	Al-Matar et al., J Rheumatol, 2002;29: 184-186.
Arthritis Arthralgia	<i>B. henselae</i>	Serol.	Al-Matar et al., J Rheumatol, 2002;29: 184-186. Hayem et al., J Rheumatol, 1996;23: 1263--1265.

Role of *Bartonella henselae* in the etiology of Henoch-Schonlein purpura.

Ayoub et al., 2002 *Pediatr. Infect. Dis J.* 21;28-31.

Henoch-Schonlein purpura (HSP) is a vasculitis with an immune pathogenesis mediated by IgA. Its etiology remains obscure.

One case with evidence of exposure to kittens and a high titer (for *B. henselae*).

Serosurvey performed on series of cases and controls. *B. henselae* antibodies in 12/18 (67%) of cases versus 8/57 (14%) controls (p< 0.0001).

Vertebral Osteomyelitis due to *Bartonella henselae* in Adults: A report of two cases.

Verdon et al., *Clin. Infect. Dis.*, 2002;35:e141-141.

- **Two adults, one HIV positive, had osteomyelitis**

28 yr-old male with fever, sweats, and upper quadrant abdominal pain, low back pain (Gardner and had a 3 mo-old kitten). Bone biopsy showed multiple foci of polymorphonuclear infiltration and medullar hyperplasia. PCR + and sero+ with *B. henselae*.

30 yr-old HIV+ man with fever, myalgia, backache and sweats was infected with *B. henselae*. Had been scratched by a kitten. Was seropositive for *B. henselae*.

- **Bone involvement is rare (about 0.1% (2/1443) to 0.3% (5/1852) OF CASES. Only 23 cases of CSD with bone involvement published, 4/23 in adults. Locations: spine (10 cases), limbs (5 cases), pelvis (2 cases), sternum (2 cases) and skull (2 cases), unknown (2 cases).**

Subacute *Bartonella* Infection in Swedish Orienteers Succumbing to Sudden Unexpected Cardiac Death or Having Malignant Arrhythmias.

Wesslen et al., 2001 *Scand. J. Infect. Dis.*, 33:429-438.

During the period 1979-92, an increasing number of sudden cardiac deaths occurred in young Swedish, male elite orienteers.

Myocarditis in 16 victims and in 4 cases also fatty infiltration mimicking arrhythmogenic ventricular cardiomyopathy (ARVC). Tissues from 5 cases tested for *Bartonella* by PCR targeting *gltA* gene.

Bartonella DNA detected in the heart of 4 deceased and lung of a fifth one. Sequences were close to *B. quintana* in 2 cases and identical to *B. henselae* in 3 cases. **Four of the 5 cases and 2 additional cases with ARVC had *Bartonella* antibodies.**

Molecular Epidemiology of *Bartonella* Infections in patients with bacillary angiomatosis-peliosis.

Koehler et al., *New. Engl. J. Med.*, 1997;337:1876-1883.

- **Of the 49 patients with bacillary angiomatosis/peliosis, 26 (53%) were infected with *B. henselae*, and 23 (47%) were infected with *B. quintana*.**
- **Subcutaneous and lytic bone lesions were strongly associated with *B. quintana*, whereas peliosis hepatis was associated exclusively with *B. henselae*.**
- **Patients with *B. henselae* infection were identified throughout the study period and were epidemiologically linked to cat and cat flea exposure ($P < 0.004$), whereas those with *B. quintana* were clustered and were characterized by low income ($P = 0.003$), homelessness ($P = 0.004$), and exposure to lice ($P = 0.03$).**



Bacillary Angiomatosis: osseous lesions

Source: Jane Koehler, UCSF

Molecular Epidemiology of *Bartonella* Infections in patients with bacillary angiomatosis-peliosis.

Koehler et al., *New. Engl. J. Med.*, 1997;337:1876-1883.

Bacillary Angiomatosis-Peliosis site according to *Bartonella* species

Site*	<i>B. quintana</i> (N=23)	<i>B. henselae</i> (N=26)	P Value (Fisher's exact test)
Skin	21	19	0.15
Lymph node	1	12	<0.001
Bone	8	0	0.001
Liver or	0	6	0.02
Liver and spleen			
Subcutaneous mass	8	1	0.008

* 24 patients had *Bartonella* infection at multiple sites

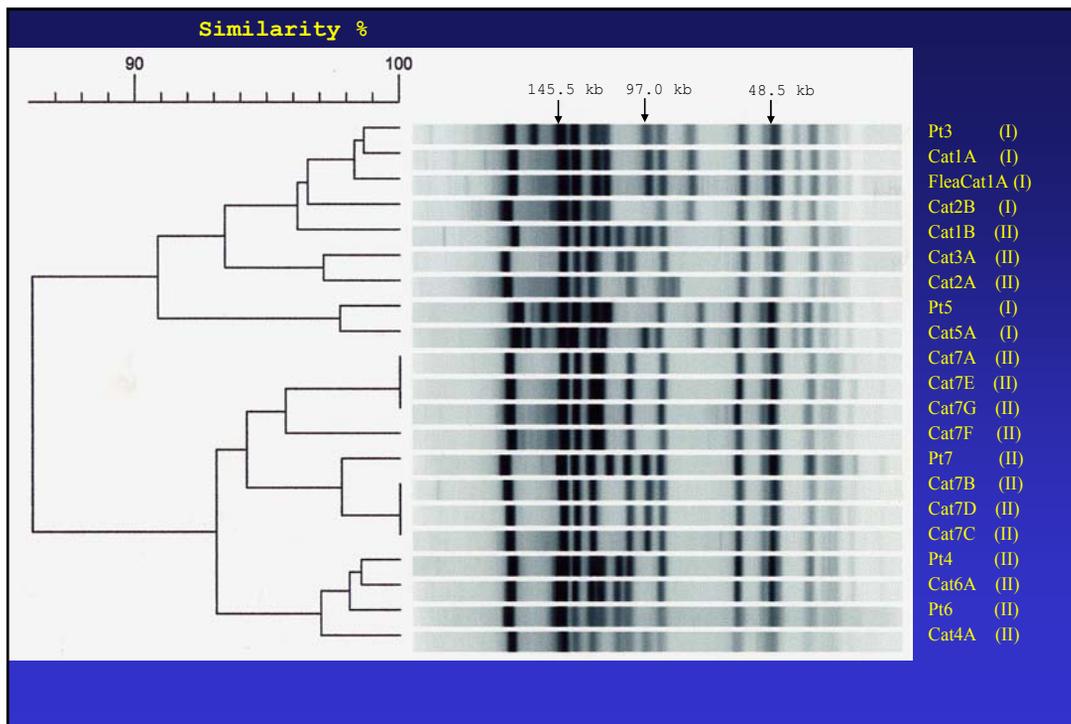
Molecular Epidemiology of *Bartonella henselae* Infection in HIV-infected patients and their cat contacts using pulsed field gel electrophoresis and genotyping.

Chang et al., *J. Infect. Dis.*, 2002, 186:1733-1739.

B. henselae was isolated from 12 HIV-infected individuals with bacillary angiomatosis/peliosis hepatis and from their 15 domestic cat contacts.

Three of the 4 patients with *B. henselae* genotype I infection, but none of the 8 genotype II patients had hepatosplenic vascular proliferative lesions ($p=0.018$).

Four of the 5 human-cat pairs had closely-related PFGE fingerprints and concordant results by 16S rDNA typing, strongly suggesting that human infection was caused by the cat contact.



Bartonella henselae infection in HIV-patients and their cats.

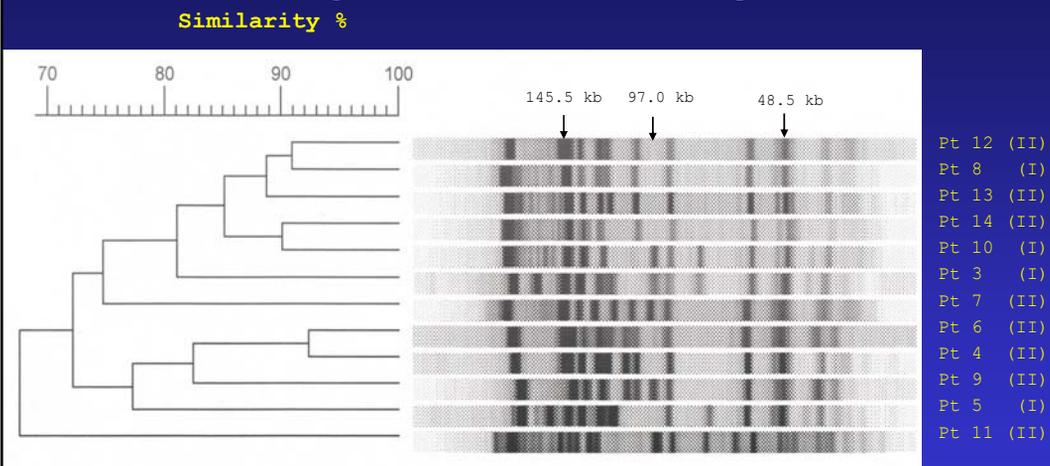
Chang et al., *J. Infect. Dis.*, 2002, 186:1733-1739.

Patient	Geno- type	Bacte- remia	Bacillary angiomatosis-peliosis lesions				
			Skin	Lymph node	Liver	Spleen	Bone
A	I	+	+	+	+	+	-
B	II	N.D.	-	+	-	-	-
C	I	+	-	-	- a	- a	-
D	II	-	+	+	- a	- a	-
E	II	+	+	-	-	-	-
F	I	+	+	-	+	+	-
G	II	+	+	+	-	-	-
H	I	+	-	-	- a	+	-
I	II	+	-	+	- b	-	-
J	II	+	-	-	- a	- a	-
K	II	-	+	+	-	-	-
L	II	N.D.	+	+	-	-	-

a= hepatomegaly and/or splenomegaly; b= granulomatous hepatitis

Molecular Epidemiology of *Bartonella henselae* Infection in HIV- infected patients and their cat contacts using PFGE and genotyping.

Chang et al., *J. Infect. Dis.*, 2002, in press.



Limited Diversity among Human Isolates of *Bartonella henselae*.

Dillon et al., *J. Clin. Microbiol.* , 2002, 40:4691-4699.

A study of 59 Australian/New Zealand isolates of *B. henselae* revealed a limited diversity among those of human origin (n=28).

Human isolates from all over eastern Australia were type I, whereas feline isolates were more likely to be type II, with less congruity of inheritance between 16S and *gltA* alleles. It was similar to previous results from the Netherlands (Bergmans et al., 1996) and Germany (Arvand et al., 2001; Sander et al., 1999).

It is suggestive that human isolates of *B. henselae* come from a limited subset of strains.

Evidence of Rodent-Associated *Bartonella* and *Rickettsia* Infections among Intravenous Drug Users from Central and East Harlem, New York City.

Comer et al., 2001 *Am. J. Trop. Med. Hyg.*, 65:855-860.

Cohort of 204 injection drug users (IDUs) from Central and East Harlem, New York City (1997-1998). Tested for seven rickettsial (*R. akari*, *R. rickettsii*, *R. prowazekii*, *R. typhi*), or *Bartonella* sp. (*B. elizabethae*, *B. henselae*, and *B. quintana*) antigens.

Highest prevalence with *B. elizabethae* (46%), 10% reacted with *B. henselae* and 2% with *B. quintana* and 9% reacted to *Rickettsia akari*.

Harlem IDUs are commonly exposed to two rodent-associated zoonotic agents.

Serosurveys of *Bartonella henselae* infection in humans in Japan.

Kumasaka et al., 2001 *Rinsho Byori*, 49 (9):906-910.

Kikuchi et al., 2002 *Microbiol. Immunol.* 46:313-316.

Kumasaka: Testing of Veterinary Professionals by ELISA: 233 Vet. Prof. From Tokyo and Chiba. Controls: negative: 155 medical students. Positive: 5 CSD cases. 15% of vet prof. seropositive. Females nearly twice as likely than males to be seropositive.

Kikuchi: Testing by IFA for *B. henselae* in 48 CSD suspects, 159 patients with cardiovascular diseases (CVD) and 129 healthy Vet. Students.

CSD suspects: 19 (39.6%) had IgG and 4 (8.3%) had IgM

Patients with CVD: 5 (3.1%) IgG +

Vet. Students: 14 (10.9%) had IgG and 1 (0.8) had IgM

Most sero+ persons had had contacts with cats.

In CSD suspects: females >> males and young >> old.

BARTONELLA SPECIES INFECTING CATS

Species	Distribution	Vector
<i>B. henselae</i>	Worldwide	Cat flea (<i>Ctenocephalides felis</i>) (Koehler et al., 1994; Chomel et al., 1996) Ticks? USA: two human cases (Lucey et al., 1992) U. K. : Seropositivity associated with <i>B. burgdorferi</i> seropositivity (n=71, r=0.43. P<0.001) (Barnes et al., 2000). <i>Bartonella</i> positive UK ticks reported.
<i>B. clarridgeiae</i>	Worldwide	Cat flea (more likely) (Raoult, person. comm.)
<i>B. koehlerae</i>	California	Cat flea (likely) (Droz et al., 1999)
<i>B. bovis</i> (<i>ex weissii</i>)	USA (Utah, Illinois)	Unknown. Cat flea?? (Regnery et al., 2000)

Bartonella sp. bacteremia prevalence in domestic cats from Western Europe

Location	N	<i>B. henselae</i>			<i>B. clarridg.</i>	<i>B. h./ B. c.</i>	Total (%)
		I	II	I/II			
Denmark (Shelter/pet cats, Chomel et al., Vet. Res., 2002)	93	1	20 (95)	0	0	0	21 (22.6)
Germany (Pet cats, Freiburg, Sander et al., J. Clin. Microbiol., 1997; *1998)	100	0	13*	0	0	0	13 (13)
Germany (Berlin, Arvand et al., J. Clin. Microbiol., 2001)	193	1	18 (90)	0	1	0	20 (10.4) (20% Strays, 1% pets)
Netherlands (Shelter cats, Sander et al., J. Clin. Microbiol., 1997)	113	6 (24)	10 (40)	0	4 (16)	5 (20)	25 (22)
France (Stray cats, Nancy, Heller et al., J. Clin. Microbiol., 1997)	94	17(34)	18 (36)	0	15 (30)	0	50 (53)
France (Pet cats, Paris, Gurfield et al., Vet. Microbiol., 2001).	436	11 (15)	36 (50)	2 (2.8)	15 (21)	8 (11)	72 (16.5)
Greece (Stray cats, Athens, Chomel et al., unpublished data)	39	2 (40)	3 (60)	0	0	0	50(13)

Bartonella henselae serosurveys in domestic cats from Europe

Country	Shelter/stray Pos./Tot. (%)	Pet Pos./Tot. (%)	Reference
Netherlands	56/113 (50%)	28/50 (56%)	Bergmans et al., J. Clin. Microbiol., 1997
Denmark	23/49 (47%)	19/43 (44%)	Chomel et al., Vet. Res., 2002
France	N. D.	179/436 (41%)	Gurfield et al., Vet. Microbiol., 2001
U. K.	33/79 (42%)	28/69 (41%)	Barnes et al., Vet. Rec., 2000
Austria	N. D.	32/96 (33%)	Allerberger et al., Eur. J. Pediatr., 1995
Germany	N. D.	107/713 (15%)	Haimerl et al., J. Med. Microbiol, 1999
Switzerland	N. D.	61/728 (8%)	Glaus et al., J. Clin. Microbiol., 1997
Sweden	N.D.	3/292 (1%)	(73/292 (25%) <i>B. elizabethae</i>) Hjelm et al., Scand. J. Infect. Dis. 2002
Portugal	N.D.	1/14 (7%)	Childs et al., Vet. Rec., 1995
Greece	32/39 (82%)	N.D.	Chomel et al., unpublished data

**Prevalence of *Bartonella* species causing bacteremia in domesticated and companion animals in the United Kingdom.
(Birtles et al., Vet. Rec. 2002;151:225-229).**

Between October 1999 and February 2000, 691 blood samples were tested for presence of *Bartonella* spp. from 615 animals .

Species	Number tested	Number of samples	Number of Pos. animals	Number of pos. samples
Cats	360	395	34	35
				30 <i>B. henselae</i> (II)
				2 <i>B. henselae</i> (I)
				2 co-infection
Dogs	211	239	0	0
Horses	27	39	0	0
Cattle	17	16	0	0

***Bartonella* sp. bacteremia prevalence in domestic cats from South-East Asia**

Location	N	<i>B. henselae</i>			<i>B. clarridg.</i>	<i>B. h./ B. c.</i>	Total (%)
		I	II	I/II			
Japan (Pet cats, Maruyama et al., J.Vet. Med. Sci., 2000)	690	43	1	0	5	1	50 (7.2)
Thailand (Stray cats/pet cats, Maruyama et al., Am. J. Trop. Med. Hyg., 2001)	275	48 (+4)	13	6	13 (9+4)	(4)	76 (27.6)
Philippines (Stray cats, Chomel et al., Am. J. Trop. Med. Hyg., 1999)	31	13 (+4)	0	0	6 (2+4)	(4)	19 (61)
Indonesia (Stray cats, Jakarta, Marston et al., Clin. Diagn Lab Immunol., 1999)	14	6 (type not specified)			3	0	9 (64)

***Bartonella* sp. bacteremia prevalence in domestic cats from The U.S.A., Australia and New Zealand**

Location	N	<i>B. henselae</i>		<i>B. clarridg.</i>
		I	II	
USA/East (Shelter/pet cats, Kordick et al., Antimicrob. Agents Chemother., 1997)	70	NA	NA	7 (10)
USA/ East		52%	48%	
USA/West		16%	84%	
Australia (pet: 16%,3/18; feral: 40%,24/59 (Sydney, Branley et al., Pathology, 1996) 342	77	35%	13.2% (pet) (Melbourne, Ng & Yates, Pathology, 1996)	0 (0)
New Zealand (Pet cats, Auckland, Joseph et al., N. Zealand Vet. J., 1996)	48	17%		0 (0)

***Bartonella henselae* bacteremia or seroprevalence in domestic cats from Africa and the Middle East**

Location	N	Bacteremia	Antibodies
South Africa	171	N.A.	23% Zimbabwe: 24% (28/119) R. S.. Africa: 21% (11/52) (Kelly et al., J. S. Afr. Vet. Ass., 1996)
	31	3.2%	0% (Bloemfontein, R.S.A.) (Pretorius et al., J. S. Afr. Vet. Ass., 1999)
Zimbabwe	25	8%	N.A. (Kelly et al., Lancet, 1998)
Israel	114	N. A.	39.5% (Baneth et al., Vet. Microbiol., 1996)
Egypt	42	N. A.	12% (Childs et al., Vet. Rec., 1995)

Acquisition of the cat scratch disease agent *Bartonella henselae* by cat fleas (Siphonaptera:Pulicidae).

Higgins et al., J. Med. Entomol., 1996;33:490-495.

- Fleas fed a concentration of 1×10^5 cfu/ml in blood were examined using IFA assay and PCR.
- Bacteria were present in the gut at 3 h, and persisted up to 9 days after infection.
- Qualitatively, the density of *B. henselae* was greater in the flea gut at day 9, indicating that replication was occurring in the gut.
- *B. henselae* was also detected in the feces of the infected fleas 9 d after infection and produced viable colonies upon inoculation onto heart infusion agar/rabbit blood plates

Experimental infection of domestic cats with *Bartonella henselae* by inoculation of *Ctenocephalides felis* feces.

Foil et al., J. Med. Entomol., 1998;35:625-628.

- Caged cat fleas were fed on 3 cats injected with 5×10^7 cfu ID and 3 cats injected with saline. Fleas were fed for 4 d, feces collected at days 2 and 4.
- Four groups of 5 cats were made:
 - Group 1: 50 *B. henselae*-exposed fleas were caged and allowed to feed on 5 cats for 6 days.
 - Group 2: flea feces collected from the 3 bacteremic cats were combined and each cat received ID 45 mg of feces suspended in 1 ml saline.
 - Group 3: 5 cats were fed 50 *B. henselae*-exposed fleas and 45 mg of feces from *B. henselae*-exposed fleas.
 - Group 4: controls (using fleas & feces from saline-injected cats).

Experimental infection of domestic cats with *Bartonella henselae* by inoculation of *Ctenocephalides felis* feces.

Foil et al., J. Med. Entomol., 1998;35:625-628.

CAT GROUPS	No. /No. Bacteremic/Exposed
<u>Group 1:</u> (infected-fleas deposited)	0/5
<u>Group 2:</u> (flea feces injected ID)	5*/5 *3/5 after 1 week *2/5 after 2 weeks
<u>Group 3:</u> (fed fleas/flea feces)	0/5
<u>Group 4:</u> (controls)	0/5

Experimental infection of domestic cats with *Bartonella henselae* by inoculation of *Ctenocephalides felis* feces.

Finkelstein et al., J. Med. Entomol., 2002;39:915-919.

- *B. henselae* can multiply in the cat flea.
- *Bartonella henselae* can persist in flea feces in the environment for at least 3 days.

**Clinical symptoms associated with natural
Bartonella henselae infection (antibodies) in domestic cats.**

Japanese cats: **Lymph node swelling:** *B. henselae* + : 13.6%,
B. henselae & FIV +: 42.9%
gingivitis: *B. henselae* + : 27.3%,
B. henselae & FIV +: 71.4%
 (Uneo et al., 1996 *Microbiol. Immunol.* 40:617-620).

Swiss cats: **Seroprevalence: 8.3% (61/728 cats)**

No difference in prevalence between healthy (7.2%) and sick cats (9.2%).

In sick cats: increased frequency of stomatitis (p=0.0117) and a variety of diseases of the kidneys and the urinary tract (p=0.0337).

There was an increased prevalence of *B. henselae* in cats positive for feline coronavirus (p=0.0185) or feline spumavirus (p=0.0235)

(Glaus et al., 1997; *J. Clin. Microbiol.* 35:2883-2885.)

**Vegetative endocarditis associated with natural
Bartonella infection in domestic cats.**

Malik et al., 1999 *J. Fel. Med. Surg.* 1:171-180.

Between 1990 and 1997, vegetative endocarditis diagnosed in six neutered cats aged between 3 and 9 years.

Diagnosis made using echocardiography (5 cases) or at necropsy (1 case).

Case	Age	Sex	Breed	Valve Affected	Culture/Histology
A	3	FN	DSH	aortic, mitral	ND
B	9	FN	DSH	aortic	<i>Bartonella</i> spp.
C	6	MN	Persian	aortic, mitral	<i>Bartonella</i> spp.
D	8	MN	DSH	aortic, ? Mitral	ND
E	6	MN	DSH	mitral, aortic	Streptococcus
F	6	FN	Tonkinese	tricuspid	Gram + cocci

No confirmation of *Bartonella* by PCR, only based on cultural aspect

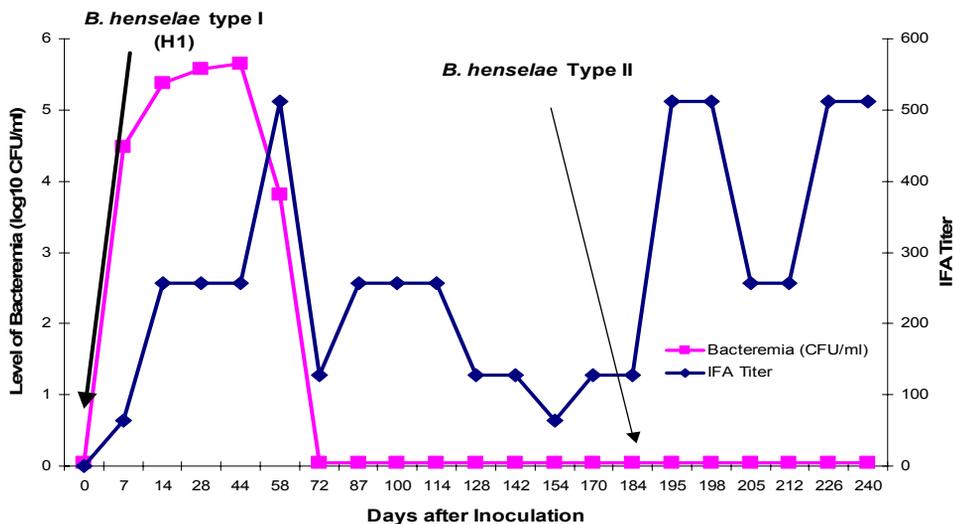
Experimental infection and re-infection of SPF cats with various strains and species of *Bartonella*.

Yamamoto et al., *Vet. Microbiol.*, 2003; 92:73-86.

Primary Infect. Strain	# bacteremic cats/ # inoculated cats	Challenge Strain	# bacteremic cats/ # inoculated cats
<i>B. henselae</i> type I (feline type I strain)	3/3	<i>B. hens.</i> Type I (Houston I strain)	0/3
<i>B. henselae</i> type I	9/9	<i>B. hens.</i> Type II	3*/9
<i>B. henselae</i> type II	6/6	<i>B. hens.</i> Type I	6/6
<i>B. henselae</i> type I	4/4	<i>B. clarridgeiae</i>	4/4
<i>B. henselae</i> type II	4/4	<i>B. clarridgeiae</i>	4/4
<i>B. clarridgeiae</i>	4/4	<i>B. hens.</i> Type I	3/4
<i>B. clarridgeiae</i>	2/2	<i>B. hens.</i> Type II	2/2
<i>B. koehlerae</i>	2/2	<i>B. hens.</i> Type I	2/2
<i>B. Koehlerae</i>	2/2	<i>B. hens.</i> Type II	2/2

* Small number of colonies: mean 8.5 CFU/ml (range: 2.6 – 17 CFU/ml)

Cross protection against re-infection by *Bartonella henselae* type II In a cat primarily inoculated with *Bartonella henselae* type I



Experimental infection and re-infection of SPF cats with various strains and species of *Bartonella*.

Yamamoto et al., *Vet. Microbiol.*, 2003; 92:73-86.

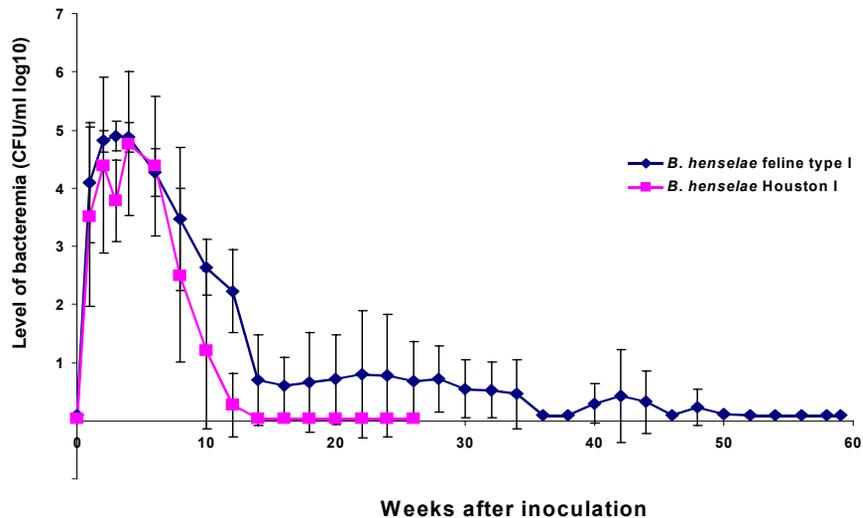
Bartonella species/Type (# cats)	Median days to reach peak bacteremia (range)	Median duration (days) of bacteremia (range)
A. PRIMARY INOCULATION		
<i>B. henselae</i> type I (n = 16)	25 (14 - 48)	80 (37 - 357)
<i>B. henselae</i> type II (n = 10)	18 (14 - 52)	181 (49 - 582)
<i>B. clarridgeiae</i> (n = 6)	36 (28 - 36)	284 (140 - 363)
<i>B. koehlerae</i> (n = 4)	36 (14 - 36)	74 (70 - 78)
Overall (n = 36)	28 (14 - 52)	98 (37 - 582)
B. CHALLENGE		
<i>B. henselae</i> type I (n = 11)	28 (22 - 48)	62 (14 - 77)
<i>B. henselae</i> type II (n = 7)	28 (14 - 35)	70 (37 - 203)
<i>B. clarridgeiae</i> (n = 8)	22 (22 - 36)	138 (43 - 405)
Overall (n = 26)	27 (14 - 48)	63 (14 - 405)

Experimental infection of SPF cats with two different strains of *Bartonella henselae* type I: A comparative study.

Yamamoto et al., *Vet. Res.*, 2002;33:669-684.

<i>B. henselae</i> Strain (# cats)	Inoculum (CFU/ml)	Fever Onset	Duration (days)	Bacteremia Duration (mean)	Relapses
feline type I (n=6)	4.8 x 10 ⁷	2-12	7-14 (mean: 5.8)	237 days	5/6 (83%)
Houston I (n=6)	6.6 x 10 ⁶ to 9.6 10 ⁷	0	0	60 days	0/6 (0%)
P value				<i>p</i> < 0.01	<i>p</i> = 0.02

Mean bacteremia level in SPF cats inoculated with *B. henselae* feline type I (n=6) and Houston I (n=6).



ARTHROPODS ASSOCIATED or POSSIBLY ASSOCIATED WITH THE TRANSMISSION OF *BARTONELLA HENSELAE*

• **Cat flea (*Ctenocephalides felis*)** (Zangwill et al., 1993; Koehler et al., 1994; Chomel et al., 1996)

• **Ticks?**

USA: Cat-related risk factors for cat scratch disease (Zangwill et al., 1993):
Ticks on humans: matched Odds ratio: 5.5 (95% Confidence interval: 1.2-25).
(21/56 cases, 5/56 controls)

Two human cases of *B. henselae* infection after tick bites (Lucey et al., 1992).

Four human co-infection Lyme/*Bartonella*, *Bartonella*-positive ticks collected on a cat and in household of a case (Eskow et al., 2001).

U. K. : Seropositivity associated with *B. burgdorferi* seropositivity (n=71, r=0.43, P<0.001) (Barnes et al., 2000).

***Bartonella* positive UK ticks reported** (Birtles, pers. comm.).

Ixodes pacificus

adult



Bartonella Infection in Dogs and association with tick-borne infections, U.S.A and Israel.

Study	Population	% seropositive to <i>B. berkhoffii</i>	Suspected vector
Pappalardo et al., 1997	Dog sera	3.6% (69/1920)	
	<i>R. rickettsii</i>	7.8% (11/141)	<i>Dermacentor variabilis</i>
	<i>E. canis</i>	36% (54/151)	<i>Rhipicephalus sanguineus</i>
	<i>B. canis</i>	57.1% (4/7)	<i>Rhipicephalus sanguineus</i>
Breitschwerdt et al., 1998	12 dogs	4/12 (33%) (serol)	<i>Amblyomma americanum</i>
	<i>E. canis</i> pos.	7/12 (58.3%) (DNA)	
	<i>E. chaffeensis</i> pos.		
Kordick et al., 1999	<i>Ehrlichia</i> +	25/27 (93%) (sero)	<i>Rhipicephalus sanguineus</i>
		18/24 (75%) (DNA)	<i>Amblyomma americanum?</i>
Baneth et al. 1998	Tick-borne Dis. suspects	4/40 (10%)	Not indicated

**MOLECULAR EVIDENCE OF *BARTONELLA* spp. IN QUESTING
ADULT *IXODES PACIFICUS* TICKS IN CALIFORNIA.**

Chang et al., *J. Clin. Microbiol.*, 2001, 39:1221-1226.

Origin	Sex	% of ticks with <i>Bartonella</i> infection (n PCR+/n tested)	
Baird Ranch	Male	0	(0/4)
	Female	0	(0/5)
Red Fern Ranch	Male	42.9	(3/7)
	Female	57.1	(4/7)
Windy Hill Open Space Reserve	Male	25.8	(17/66)
	Female	8.1	(5/62)
Total		19.2	(29/151)

**MOLECULAR EVIDENCE OF *BARTONELLA* spp. IN QUESTING
ADULT *IXODES PACIFICUS* TICKS IN CALIFORNIA.**

Chang et al., *J. Clin. Microbiol.*, 2001, 39:1221-1226.

Origin	# Ticks	PCR-RFLP profile	Closest <i>Bartonella</i> species*
Red Fern Ranch	3	<i>B. quintana</i> -like	<i>B. quintana</i> (97.8% – 100%)
Windy Hill Open Space Reserve	6	<i>B. henselae</i> -like	<i>B. henselae</i> (97.4%-100%)
	5**	<i>B. bovis</i> -like	<i>B. bovis</i> (99.3%-99.6%)
	1***	<i>B. vins. berkhoffii</i>	<i>B. vins. Berkhoffii</i> (98.9%)
	3	Unrecognized	<i>B. washoensis</i> (99.3%-100%)
	11	Bart. co-infection	unconclusive

*% DNA similarity based on 273 bp of the *gltA* gene; ** one mixed infection *B. bovis*/*B. henselae*; *** mixed infection *B. vins. berkhoffii* /*B. henselae*

Concurrent Infection of the Central Nervous System by *Borrelia burgdorferi* and *Bartonella henselae*. Evidence For a novel tick-borne disease complex.

Eskow et al., Arch Neurol., 2001;58:1357-1363.

Subjects: Two male patients (14 and 36 years old) and 2 female patients (15 and 30 years old) with a history of tick bites and Lyme disease.

Results: . Patients living in Lyme-endemic area of New Jersey, with chronic Lyme disease symptoms (neuroborreliosis).
 . Seropositive for *Bartonella henselae*. *B. henselae* DNA detected in patients' blood.
 . DNA of *B. henselae* and *Borrelia Burgdorferi* in CSF.
 . *B. henselae* DNA detected in live deer ticks obtained from the households of 2 of these patients.

Detection of *BARTONELLA* spp. from 228 Pooled Tick Samples by PCR of the *gltA* Gene, California (1996-1997).

Chang et al., Comp. Immunol. Microbiol. Infect. Dis., 2002, 25:229-236.

County	Tick Species			
	<i>Ixodes</i> sp.		<i>Dermacentor</i> sp.	
	N. pools*	N Pos. (%)	N. pools	N. Pos.(%)
Shasta	13 Adults	1 (7.7%)	N. A.	
Sonoma	62 Adults	8 (12.9)	N. A.	
	10 Nymphs	1 (10.0)	N. A.	
El Dorado	24 Adults	4 (16.7)	1	0 (0)
Los Angeles	63 Adults	0 (0)	N. A.	
Orange	36 Adults	8 (22.2)	19	2 (10.5)
			<i>D. occidentalis</i>	1/12 (8.3)
			<i>D. variabilis</i>	1/7 (14.3)

* pool = up to 5 ticks/pool

Bartonella Infection in Domestic Dogs, U.S.A.

Bartonella species

Clinical signs

B. vinsonii subsp. *berkhoffii*

Endocarditis, Arrhythmias,
Myocarditis, Granulomatous Rhinitis
and Granulomatous Lymphadenitis.

B. henselae

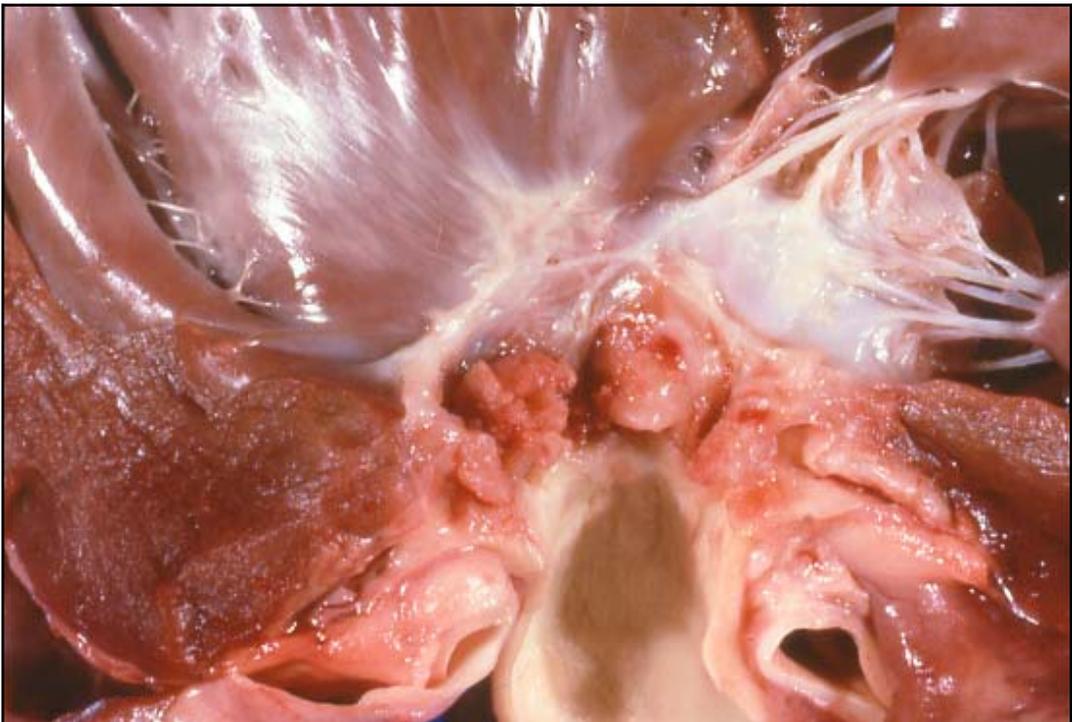
Peliosis hepatis, Granulomatous
hepatitis, hepatic lesions

B. henselae &
B. elizabethae

Non specific clinical abnormalities
(severe weight loss, protracted
lethargy, anorexia & chronic disease
course

B. clarridgeiae
B. washoensis

Endocarditis, hepatic lesions
Endocarditis



***Bartonella* spp. Endocarditis Case-Control Study in U.S. Army Dogs (from A.F.I.P. archives).**

Materials and Methods:

- **CASES:** 25 dogs with histopathological diagnosis of endocarditis.
- **CONTROLS:** 28 dogs with history of hip dysplasia, no lymphoplasmatic changes on histopathology of cardiac tissue.
- **Histopathology:** H & E, Warthin-Starry silver staining
- **DNA extraction (Qiagen Kits)**
- **PCR/RFLP of citrate synthase (*gltA*) gene (*TaqI*, *HhaI*, *AccI* and *MseI* endonucleases)**
- **Partial sequencing of citrate synthase gene**

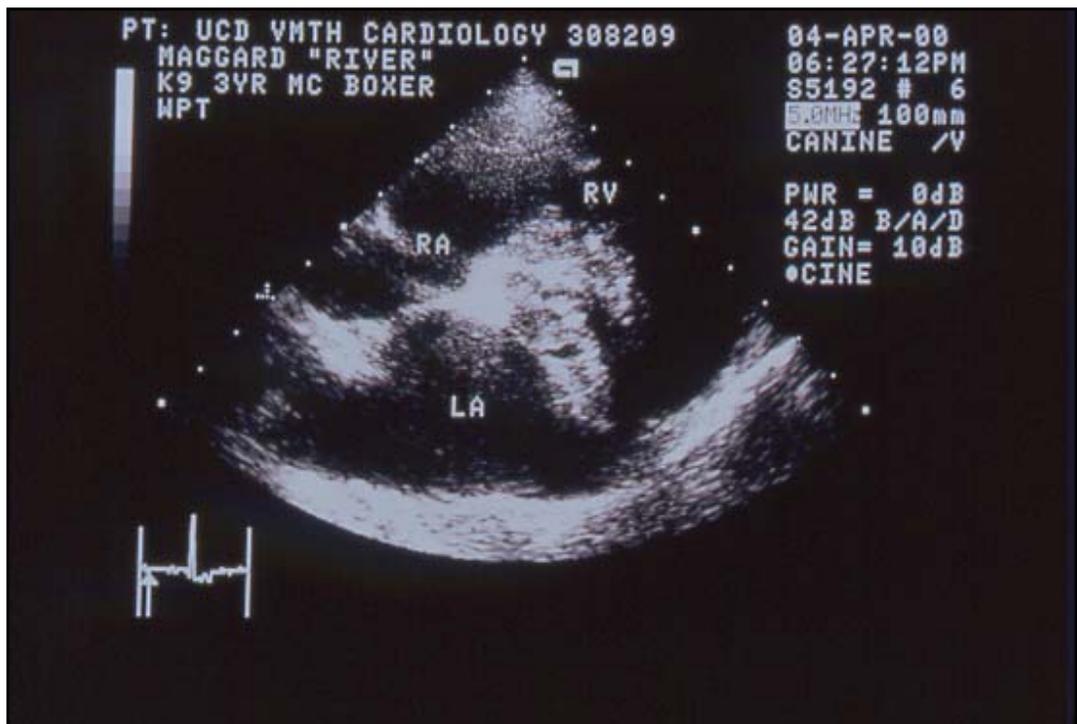
***Bartonella* spp. Endocarditis Case-Control Study in U.S. Army Dogs (from A.F.I.P. archives).**

RESULTS:

- **CASES:** 73.0% (19/26 dogs) PCR Positive
- **CONTROLS:** 3.6% (1/28 dogs) PCR weak Positive
- **Histopathology:** 20% (4/20) had visible organisms with Warthin-Starry silver staining
- **PCR/RFLP of *gltA* gene and partial sequencing of the gene: several profiles or sequences, including**
 - **6 *B. vinsonii berkhoffii*** (2 from Thailand, 1974; 4 from USA (Bethesda, MD, 1978; San Antonio, TX, 1978 and 1986; Puerto Rico, 1987)
 - **8 *B. henselae*-like** (mainly Vietnam, 1970-1972)
 - **1 *B. clarridgeiae*-like (Type C)** (Germany 1988).
 - **2 *B. washoensis* (Type D)** (Guam, 1992; Germany, 1995)
 - **2 mixed infections** (Okinawa, 1970; Florida, 1986)

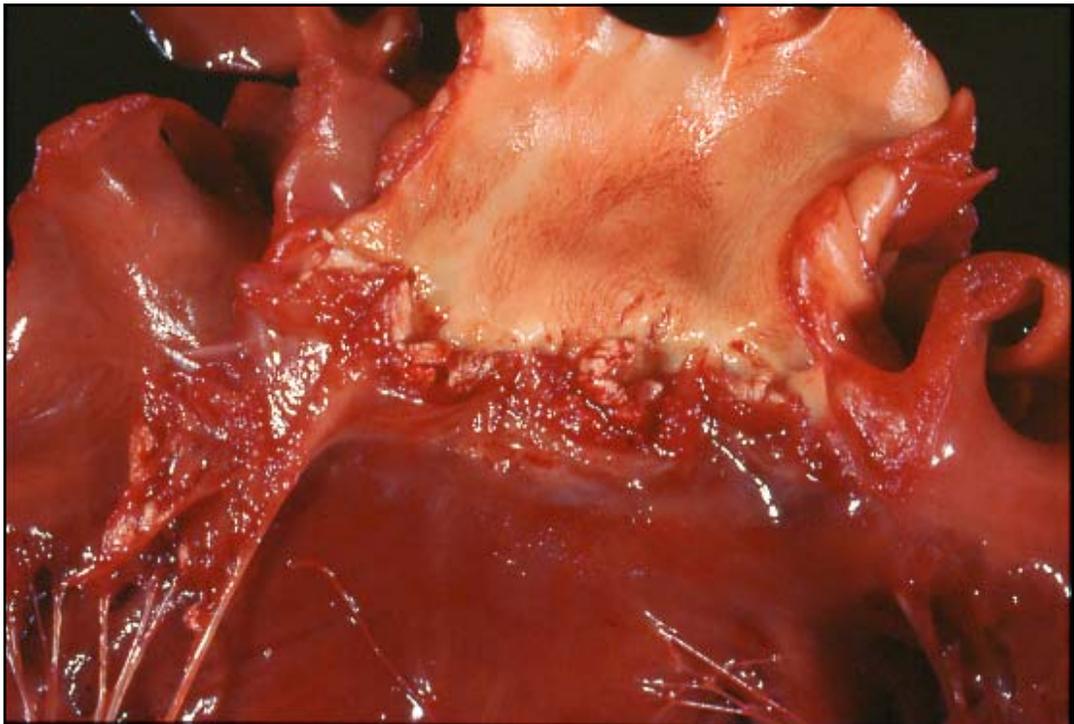
**Clinical Symptoms and Etiology of Dog Endocarditis Cases,
U.C. Davis, VMTH, 1999-2001. McDonald et al., in preparation.**

18 dogs, all medium to large breed, median weight		N (%)
Presenting complaint:	lameness	8 (44%)
	lethargy	6 (33%)
	anorexia	6 (33%)
	respiratory problems	4 (22%)
	weakness	3 (17%)
Valve involvement:	aortic	9 (50%)
	mitral	8 (44%)
	aortic and mitral	1 (6%)
Etiology:	Unknown	6 (33%)
	<i>Bartonella</i>	5 (28%)
	<i>Staphylococcus aureus</i>	3 (17%)
	<i>Streptococcus canis</i>	2 (11%)
	<i>Pseudomonas aeruginosa</i>	1 (6%)
	<i>Escherichia coli</i>	1 (6%)



Clinical Cases of Dog Endocarditis, U.C. Davis, 6/1999-5/2001

ID#	Date	Age	Sex	Breed	Valve	<i>Bartonella</i>			<i>A. pha</i>
						serol	Cult	PCR	Serol
1	6/99	7 y	MN	Bernese	Aortic	Neg	Neg	NA	Neg
2	11/99	14 y	FS	Australian	Mitral	Neg	Neg	NA	Neg
3	12/99	14 y	FS	Shetland	Aortic	Neg	Neg	NA	Neg
4	1/00	9 y	MN	Shepherd	Aortic	1024	Neg	+(Bc-l)	1:160
5	3/00	10y	MN	Labrador	Mitral	Neg	Neg	NA	Neg
6	4/00	2.5 y	MN	Boxer	Aortic	2048	+(B.c.)	+(B.c.)	1:100
7	6/00	9y	MN	Germ. Shep.	Mitral	Neg	Neg	NA	Neg
8	6/00	4 y	MN	Red Hound	Mitral	Neg	Neg	NA	Neg
9	10/00	8 y	FS	Germ. Shep.	Mitral	32/64	Neg	NA	Neg
10	10/00	5.5 y	M	Labrador	Aortic	Neg	Neg	NA	Neg
11	12/00	6 mo	F	Great Dane	Aortic	Neg	Neg	NA	Neg
12	1/01	7 y	M	Bull Mastiff	Aortic	1024	Neg	+(Bvb)	1:640
13	1/01	6 y	MN	Airedale	Aortic	1024	Neg	+(Bvb)	1:320
14	1/01	12 y	MN	Golden retr.	Mitral	Neg	Neg	NA	1:80
15	2/01	10 y	MN	Labrador mix	Aortic	4096	Neg.	+(Bvb)	1:100
16	3/01	9y	MC	Shepherd mix	M&A	Neg	Neg	Neg	Neg
17	4/01	6.5y	FS	Bull Mastiff	Mitral	256 (Bc)	Neg	Neg	Neg
18	5/01	8y	FS	Golden retr.	Mitral	Neg	Neg	Neg	Neg



Bacterial endocarditis and *Bartonella* endocarditis cases: Comparison in humans and dogs.

	Humans %	Dogs %
Bacterial endocarditis		
Culture neg. infect. endoc.	14 (88/620)	27
Aortic Valve	43-47	23
Mitral Valve	47-57	67
Pre-existing valvular disease	30	unlikely
<u>Bartonella positive endocarditis</u>		
Aortic	88 (29/33)	71.4 (5/7)
Mitral	12 (4/33)	14.3 (1/7)
Mixed	6 (2/33)	14.3 (1/7)
Pre-existing valvular disease	53 (8/15)	unlikely

Bartonella spp. identified in 26 positive dogs with endocarditis, A.F.I.P. and U.C. Davis, USA

Species Positive	Culture %	AFIP (N=19)		UCD (N=7)	
		(n)	%	(n)	
<i>B. vinsonii</i> subsp. <i>berkhoffii</i>	0	31.6	(6)	57	(4)
<i>B. henselae</i> -like	0	42.1	(8)	0	(0)
<i>B. clarridgeiae</i>	1	0	(0)	14.3	(1)
<i>B. clarridgeiae</i> -like (type C)(<i>gltA</i> sequence identical to isolates from raccoons, 25% of California raccoons bacteremic)	0	5.3	(1)	14.3	(1)
<i>B. washoensis</i> (type D)	1	10.5	(2)	14.3	(1)
Mixed infection	0	10.5	(2)	0	(0)

***Bartonella* spp. Valvular Endocarditis in Dogs Necropsied at
U.C. Davis (1997-2001).**

(Pasavento et al., in prep.)

- **31 necropsied dogs with valvular endocarditis during the 5-year period.**
 - **Routine blood culture positive for 10 dogs, including *E. coli*, *Pseudomonas aeruginosa*, Beta-hemolytic streptococci and *Staphylococcus* spp.**
 - ***Bartonella* DNA detected by PCR (primers directed at citrate synthase gene) on 12 (38.7%) of these 31 dogs.**
 - **2 dogs also blood culture positive for other pathogens**
 - **10 dogs blood culture negative.**
- mean (range) age: 9 (1-16) yrs; 9/12 intact/neutered males
5/12 had history of polyarthritis or swollen joints.**

**Detection of *Bartonella henselae* and *B. clarridgeiae* DNA
in hepatic specimens from two dogs with hepatic disease.**

Gillepsie et al., JAVMA., 2003;222:47-51.

- **4-year-old spayed female Basset Hound: 6 month history of recurrent fever, anorexia, weight loss. High hepatic enzyme activity, pyogranulomatous inflammation of the liver. PCR + for *B. henselae*.**
- **6-year-old female spayed Doberman Pinscher: High hepatic enzyme activity. Liver biopsy: moderate to severe lymphocytic hepatitis. PCR + for *B. clarridgeiae*.**

Bartonella henselae and *B. elizabethae* as Potential Canine Pathogens.

Mexas AM, Hancock SI & Breitschwerdt EB., J. Clin. Microbiol., 2002;40:4670-4674.

- Four dogs with nonspecific clinical abnormalities, such as severe weight loss, protracted lethargy, and anorexia, in addition to a chronic disease course.
- 3/4 dogs had *B. vinsonii berkhoffii* antibodies.
- **Blood:** PCR + (16S-23S rDNA) for *B. henselae* in 3 dogs, PCR + for *B. elizabethae* in one dog.

Conditions caused by *Bartonella henselae* in humans, cats and dogs, and by *B. vinsonii berkhoffii* in dogs.

Conditions	Humans	Cats	Dogs
Chronic bacteremia	+	++	+
Lymphadenitis,granulomatous rhinitis and lymphadenitis	++	+	++
Bacillary Angiomatosis/Peliosis	++	-	+
Endo/Myocarditis, Arrhythmia	++	+	++
Prolonged fever	+	-	+/-
Lethargy, weight loss, anorexia	?	+/-	+
Neurological symptoms	++	+/-	+
Encephalitis	+	?	+/-
Arthritis, joint pain	+	?	+
Glomerulonephritis	+	+/-	?
Uveitis and ocular lesions	+	+	+
Reproductive disorders	?	+	?

CONCLUSIONS

- *Bartonella* species are a major source of infectious endocarditis in dogs. Localization and type of lesions are very similar in humans and dogs, but dogs present a higher prevalence of *Bartonella* endocarditis and a larger number of *Bartonella* species involved.
- *B. vinsonii* subsp. *berkhoffii* infection is widespread in many parts of the USA and in several countries in Asia and Europe. Infection appears to be more frequent in warm climates. *B. vinsonii berkhoffii* infected dogs are more likely to be sero-positive for tick-borne infections, especially *Ehrlichia* spp., and ticks have been found to harbor *Bartonella* spp. DNA, including *B. vinsonii berkhoffii*.
- The clinical spectrum of *Bartonella* infection in dogs is expanding and more likely to be not only identical, but also as diverse to what has been observed in humans.